Mitochondrial-Derived Oxidants and Cellular Responses to Low Dose/Low LET Ionizing Radiation

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Exposure of cells to ionizing radiation (IR) results in the immediate formation of free radicals that last a matter of milliseconds and it has been assumed that the subsequent biological effects of IR are due to the initial damage caused by these free radicals. However, it is becoming increasingly clear that intracellular metabolic oxidation/reduction (redox) reactions can be affected by IR and remain perturbed for long periods of time. These metabolic redox reactions have been suggested to contribute to the effects of low dose IR. Mitochondrial electron transport chain (ETC) complexes believed to be major contributors to metabolic redox reactions via $O_2^{\cdot-}$ and H_2O_2 production include: Complex I (or NADH dehydrogenase), Complex II (succinate dehydrogenase), and Complex III (ubiquinone-cytochrome c oxidoreductase). If IR exposure induces disruptions in the proper assembly and/or function of mitochondrial ETCs (either by causing mutations or directly altering the protein structure/activity), an increase in residence time and/or accessibility of reduced components of the ETCs to O_2 could result in an increase in the probability of one-electron reductions of O_2 to form reactive oxygen species (ROS; i.e., $O_2^{\cdot-}$ and H_2O_2). The resulting increased fluxes of $O_2^{\cdot-}$ and H_2O_2 could then lead to a condition of metabolic oxidative stress that could continue to cause oxidative damage long after IR exposure. If IR-induced damage (and/or damage caused by metabolic oxidative stress), resulted in mutations to either mitochondrial or nuclear DNA coding for genes required for the proper assembly or function of ETCs, this condition of metabolic oxidative stress could also become a heritable trait. Therefore, this mechanism could potentially contribute to IR-induced genomic instability that persists for many cell generations. Since ROS have also been strongly implicated in mitogenesis and genomic instability, which are thought to contribute to the initiation, promotion, and progression of carcinogenesis, it has been proposed that metabolic oxidative stress contributes to the deleterious effects of low dose ionizing radiation. Despite the circumstantial evidence that radiation exposure results in metabolic oxidative stress that contributes to radiation-induced genomic instability, relatively little is known about the intracellular sources of ROS.

Results from the Spitz lab demonstrate that Chinese hamster fibroblasts carrying mutations in Succinate Dehydrogenase subunit C (SDHC) demonstrate increased mitochondrial ROS production, increased genomic instability, and increased sensitivity to low dose/low LET ionizing radiation. Furthermore, over expression of superoxide dismutase and/or catalase inhibits low dose radiosensitivity in cells expressing the SDHC mutation, showing that mitochondrial $O_2^{\cdot-}$ and H_2O_2 contribute to the effects of low dose/low LET radiation. In another set of studies genomically unstable cells isolated following ionizing radiation were found to demonstrate significant disruptions in mitochondrial metabolism, increased ROS production, and these effects could also be suppressed by over expression of cellular antioxidants. Overall the results to date demonstrate that mutations in genes coding for mitochondrial ETC proteins can cause increased ROS production, metabolic oxidative stress, genomic instability, and sensitivity to low dose IR. These results provide supporting evidence for the speculation that radiation-induced mutations to genes coding for mitochondrial ETC proteins can significantly contribute to the persistent biological effects seen following exposure to ionizing radiation.

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